INFLUENCE OF SYSTEMIC INFLAMMATORY RESPONSE TO APPEARANCE OF NEW FOCI OF CHRONIC INFLAMMATION

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UTICAJ SISTEMSKOG INFLAMATORNOG ODGOVORA NA POJAVU NOVIH ŽARIŠTA HRONIČNE INFLAMACIJE

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ABSTRACT

Changes in the body in the presence of a chronic inflammatory process, even of a low intensity, lead to the change in the body's reactivity, having a negative impact on the development, course and clinical prognosis of newly emerging inflammatory processes. Structural changes in the vascular network in the focus of chronic inflammation and following cellular reactions that occur under the action of chemokines and cytokines are the basis for the maintenance and development of the phlogogenic process, including subsequent structural changes in tissues. The failure to resolve the inflammation leads not only to the persistence of the process in the primary focus, but also to the formation of a multitude of the so-calledpathological circles, included at the system level, causing the imbalance among proinflammatory, anti-inflammatory and pro-resolving factors. As a result, conditions are formed for the emergence of new foci of the inflammation in other organs and tissues and in the case of their realization, new vicious circles are formed that contribute to the maintenance and progression of the inflammation. The complex application of etiotropic, pathogenetic and sanogenetic principles of the treatment allows intensifying of the formation of specialized pro-resolving factors with the elimination of their relative insufficiency, contributing to the reduction of newly formed vessels and to the restoration of the normal cellular composition of the tissue as well as to the resolution of inflammation.

***Keywords**: specialized permissive mediators, chronic cytokine response, imbalance of counter-regulatory factors*

SAŽETAK

Promene u telu u prisustvu hroničnog inflamatornog procesa, čak i malog inteziteta, dovode do promene u reaktivnosti tela i imaju negativan uticaj na razvoj, tok i kliničku prognozu novih inflamatornih procesa. Strukturne promene u vaskularnoj mreži u žarištu hronične inflamacije koje prate ćelijske reakcije koje nastaju pod dejstvom hemokina i citokina su osnova za uspostavljanje i razvoj flogogenog procesa, uključujući sledeće strukturne promene u tkivima. Neuspeh da se reši problem inflamacije dovodi ne samo do postojanosti samog procesa u primarnom žarištu već i do stvaranja mnoštva takozvanih patoloških promena uključenih na sistemskom nivou, prouzrokujući disbalans između proinflamatornih i anti-inflamatornih faktora. Kao rezultat toga, javljaju se uslovi za nastanak novih žarišta inflamacije u drugim organima i tkivima i u slučaju njihovog ostvarenja, novi začarani krugovi nastaju koji doprinose održavanju i napredovanju inflamacije. Kompleksna primena etiotropnih, patogenetskih i sanogenetskih principa lečenja omogućava pojačano stvaranje specijalnih anti-inflamatornih faktora uz eliminaciju njihove relativne insuficijencije, doprinosi redukciji novo formiranih sudova i obnovi normalnog ćelijskog sastava tkiva kao i suzbijanju inflamacije.

***Ključne reči:** specijalni permisivni medijatori, hronični citokini odgovor, disbalans kontra regulatornih faktora*

ABBREVIATIONS

OA - osteoarthritis
PAMP - pathogen-associated molecular pattern
DAMP - damage-associated molecular pattern
SPM - specialized pro-resolving mediators
PRR - pattern recognition receptors
TLR - toll-like receptors
NLR - nod-like-receptors
TNF - tumor necrosis factor

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INTRODUCTION

There are people who get sick very rarely, for example, due toviral infections. At the same time, other people regularly get sick due to any randomly encountered viral infection, and their disease usually lasts for a long time, with complications. This happens most often in patients with comorbid pathology.

In the modern world, there are more and more patients with comorbid pathology. In such patients, with the appearance of a new, for example, somatic disease with the standard approach to its treatment, there is a high probability of transition to the chronic form of the course. In this connection, their choice of tactics and scope of medical measures become more complicated, including the subsequent period of time with an exacerbation of the course of one of the diseases. Thus, the prognosis for the complete cure of acquired diseases is constantly deteriorating.

Many researchers recognize that subclinical manifestations of the low-intensity inflammatory process, for example, in osteoarthritis, have a significant negative impact on the prognosis of this disease [20].

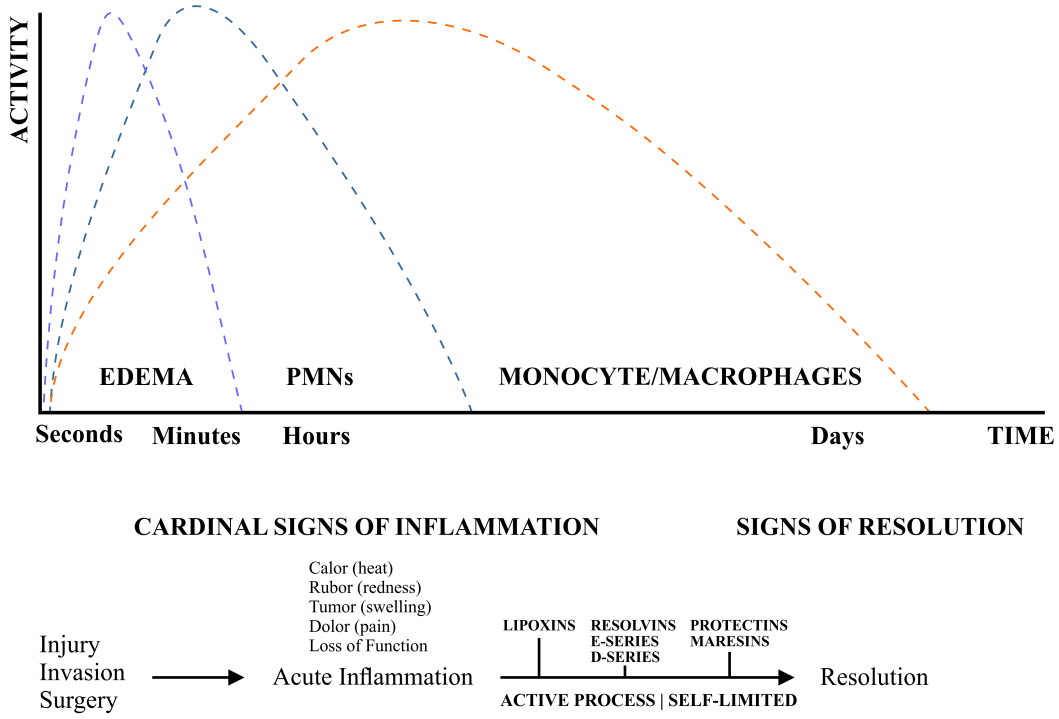
An attempt to systematize the accumulated experience on the influence of chronic inflammation in the body on the appearance of new foci and maintaining the course of the inflammatory process in them was the basis for writing this article.

RESEARCH ON THE EFFECTS OF SYSTEMIC INFLAMMATORY RESPONSE

Modern studies of the development mechanisms of many socially significant diseases have shaped the idea that their pathogenetic basis is a chronic systemic inflammation. The list of these comorbid forms of pathology is quite large including diseases of the cardiovascular system (atherosclerosis, myocardial infarction, stroke, etc.), obesity, neurodegeneration, type 2 diabetes, depression, oncology chronic kidney disease, chronic lung disease, etc. (22, 24, 28).

It is known that the development of acute inflammation occurs under a fairly tight control of counter-regulatory factors that function according to the principle of negative feedback, ensuring the coordination of phases of this adaptive response in time (5). In this case, it is customary to distinguish the initiation phase and the resolution phase (Figure 1).

Figure 1. Structure and functions of proinflammatory mediators



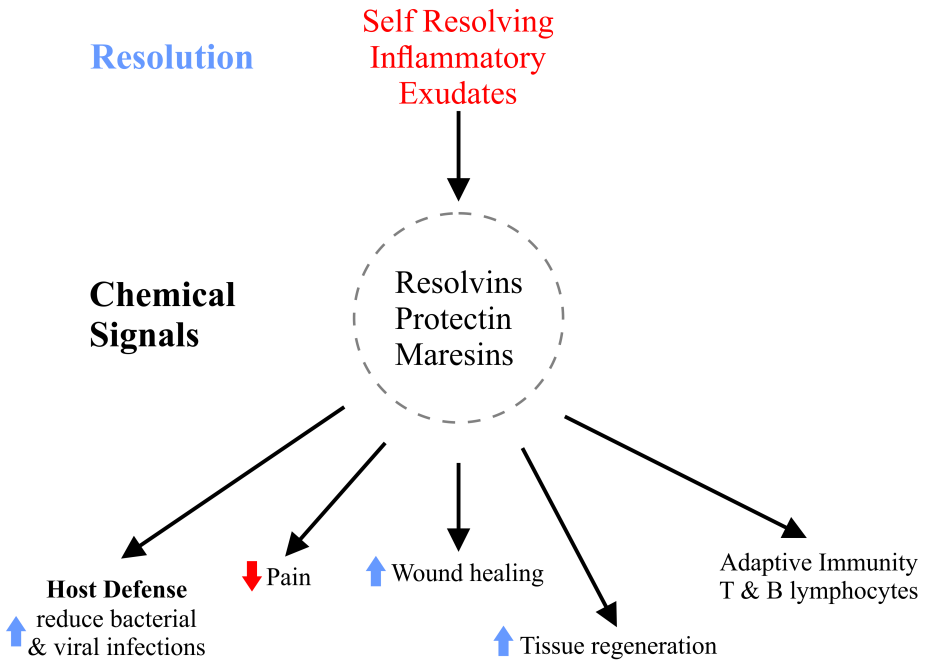
Acute inflammation was formed by an evolutionary protective-adaptive response, aimed not only to eliminate the cause, but also to eliminate the consequences of its effect, i.e. for the restoration of damaged tissues, it is strictly limited and leads to a complete resolution, which allows the return to homeostasis (25). In this regard, recently, the interest of researchers has been focused on the study of the mechanisms of flow of the resolution phase. According to the data obtained, it is the activity of development of the resolution phase that largely determines the outcome of inflammation and the restoration of function at the tissue level. C.D. Buckley, D.W. Gilroy, C.N. Serhan (2014) (4) consider the main events in this process:

1. Removal of the pathogen-associated molecular pattern (PAMP) and the damage-associated molecular pattern (DAMP).
2. Destruction of proinflammatory mediators and blockage of ways to implement their actions.
3. Suppression of emigration of polymorphonuclear leukocytes and their apoptosis.
4. Recruitment of alternatively activated macrophages for participation in efferocytosis and removal of debris.
5. Restoration of the structural integrity and normal cellular composition of the tissue.

By replacing the previous ideas that inactivating proinflammatory inflammatory mediators are enough to complete it, the understanding has emerged that resolving inflammation is a complex, coordinated, actively proceeding and controlled process. At the same time, G. Fredman, I. Tabas (2017) in their review, state (Figure 2) (12), that the resolution process is controlled by endogenous mediators of different chemical nature:

1. Specialized pro-resolving mediators (SPM), which include lipoxins, resolvins, protectins and maresins.
2. Protein mediators, such as annexin A15 and IL-10.
3. Gases, primarily carbon monoxide (CO) and hydrogen sulfide (H2S).
4. Nucleotides, such as adenosine and inosine.
5. It is quite obvious that the resolution mediators have not only local, but also the systemic effects.

Figure 2. The interaction of factors of the inflammatory process

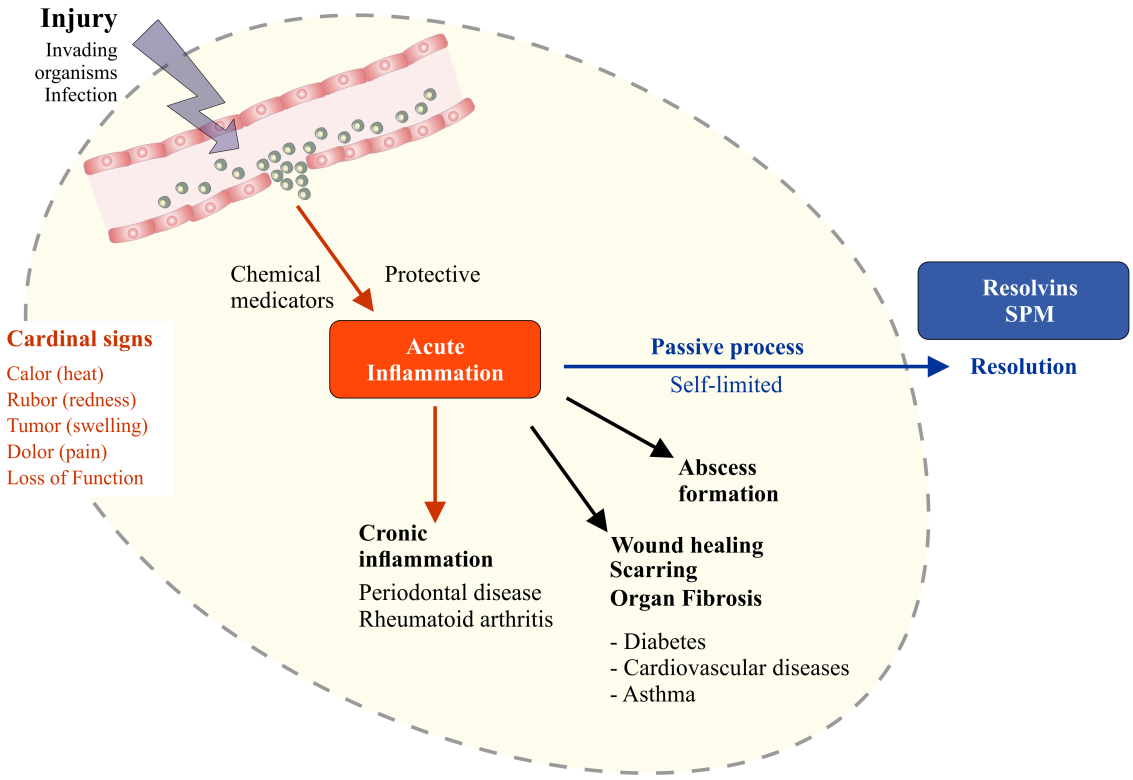


Resolution SPM signal links to system needs

From the above mentioned, it follows that various violations in the management or implementation of the system resolution mechanisms will lead to local "deficiency" of this phase in the foci of inflammation of any localization. Depending on the severity of this "deficiency", it can lead to various negative consequences: an increase in the duration of the process, up to the onset of chronic inflammation, and deterioration in the result of this protective-adaptive reaction, for example, in the form of scar tissue formation, fibrosis and dysfunction of the organ or tissue.

Imbalance of these two groups of the physiological processes, proinflammatory on the one hand, anti-inflammatory and resolving inflammation on the other, with insufficiency (absolute or relative) of resolution permissions mechanisms forms the basis of any chronic inflammation (22, 27), (Figure 3).

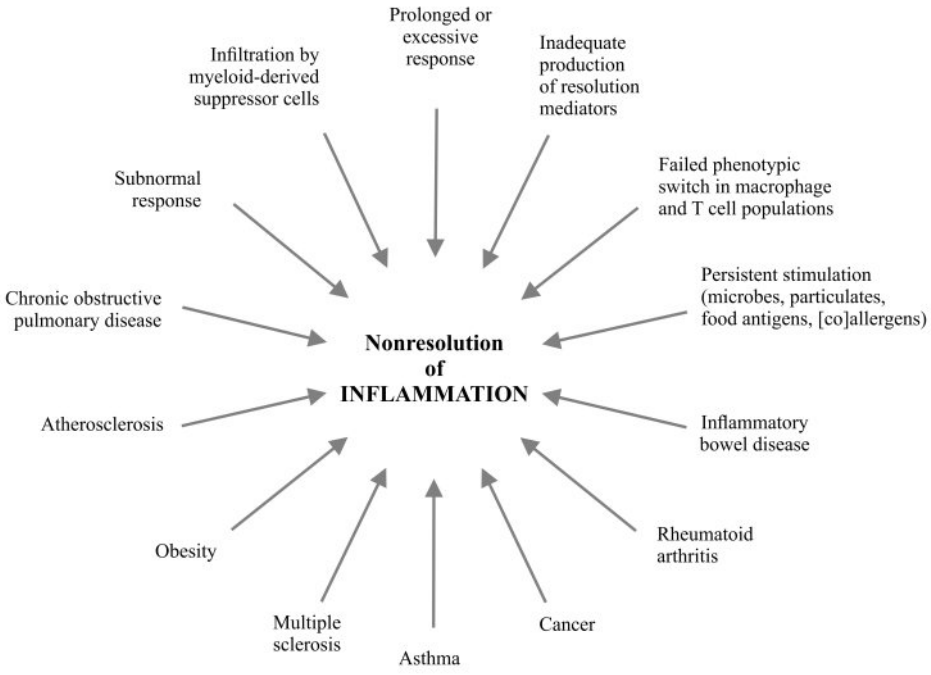
Figure 3. Ways to resolve acute inflammation



The duration and severity of inflammation are determined by the interaction (that is, the efficiency and consistency of the flow of multidirectional processes): on the one hand, there is an increase in the phlogogenic reaction aimed at isolating and eliminating the cause, and on the other hand, their restriction of inflammation and tissue repair. The overall magnitude and duration of inflammation depend on competing physiological processes, namely, on pro-inflammatory mechanisms that enhance the programs of inflammation and endogenous inhibition, which in turn control the resolution of inflammation (28). Thus, the imbalance with a predominance of pro-inflammatory phenomena may develop as a result of relative or absolute insufficiency of anti-inflammatory factors and mechanisms that allow inflammation.

The predominance of pro-inflammatory effects may develop despite the opposition of anti-inflammatory and inflammatory factors controlling the severity of their self-limiting mechanisms. The imbalance between the groups of counter-regulatory factors with a predominance of pro-inflammatory over anti-inflammatory and final inflammation is typical for the formation of a chronic variant of the course of inflammation and may develop due to many reasons (15, 25), (Figure 4).

Figure 4. Type of chronic (unresolved) inflammation



The totality of reasons for the unresolved process is united by the occurrence of absolute or relative insufficiency of the mechanisms of the resolution phase of inflammation. Modern researchers have focused on the regulators of the resolution of inflammation, known as "specialized pro-resolving mediators", due to the emergence of the ability to control the process of inflammation through drug and non-medication effects on the "target". There is an active process of accumulating data that the insufficiency of one or the other specialized permitting mediator (SPM) just plays a crucial role in the emergence of a range of socially significant diseases: atherosclerosis and other cardiovascular diseases, osteoarthritis, obesity, type 2 diabetes, chronic obstructive diseases of the lungs, ulcerative colitis, tumors, and so on (24). Disruption of the resolution mechanisms, in turn, can be caused by the following factors: nutritional deficiency of essential fatty acids (EPA eicosapentaenoic acid, DHA docosahexaenoic acid) that are substrates for specialized pro-resolving mediators, polymorphism of enzymes involved in their synthesis, irregularity when receiving specialized pro-permit mediators, etc. Thus, such a typical phenomenon as the coexistence of a whole spectrum of diseases in one patient, united by a common pathological process, becomes understandable and justified.

The generality of the pathogenesis of comorbid forms of pathology suggests a pattern of dissemination of such foci of chronic non-infectious inflammation with a sufficiently long non-resolution of this process. The initially developed inflammatory focus is limited, but if the inflammation is not resolved and continued, against the background of the organism's altered reactivity due to the development of systemic phenomena, conditions are created for the emergence of new "lesions". The complex of systemic phenomena that occurs under the action of cytokines is well known as the acute phase response, or the "pre-immune response". Common manifestations of the inflammation include hyperthermia, arthralgia and myalgia, sleep disturbances, loss of appetite, changes in functioning of the physiological systems (respiration, circulation, digestion, urination, etc.), as well as changes in the laboratory parameters: an increase in the erythrocyte sedimentation rate, leukocytosis, dysproteinemia (C-reactive protein, amyloid-A and P, transferrin, ceruloplasmin, immunoglobulins, enzymes, etc.) (14). The purpose of these reactions is to restore homeostasis and eliminate the cause of its violation, however, with the unresolved inflammation and its continuation, these phenomena can cause alteration of other tissues and organs, accompanied by the development of low-intensity (mild) inflammation in them, with the appearance of disorders of their function, which, it would seem, have no connection with the site of the initial lesion (3). As a result, even minor changes in the tissue with the formation of DAMP under normal conditions, that is, an event that occurs constantly, can lead to the emergence of a new independent chronic source of inflammation and the production of pro-inflammatory factors.

The progress in understanding the pathogenesis of osteoarthritisassociated with advances in molecular biology, discovered that the mediators of acute phase inflammatory response cytokines and prostaglandins are able to activate chondrocytes, which in turn increase the production and secretion of metalloproteinases that destroy cartilage and participate in the formation of alarminov (a molecular fragment associated with the damage of DAMP) such as fibronectin, hyaluronan, soluble heparan sulfate, β-defensin-2 and protein

groups with high mobility. In turn, DAMP, through the interaction with the pattern recognition receptors (PRR), such as toll-like receptors (TLR) on the surface of immune cells or with PRR in the cytoplasm of cells (nod-like-receptors (NLR)), activate the mechanisms of the innate immune response and trigger the development of non-infectious inflammation (16, 19).

For example, according to K.A. Scheibner, M.A. Lutz, S. Boodoo, M.J. Fenton, J.D. Powell, M.R. Horton (2006) (20), the resulting low molecular weight hyaluronan mediated by toll receptors, activates the expression of inflammatory genes in epithelial cells, endothelial cells, fibroblasts, dendritic cells and macrophages. The activated genes are responsible for chemokine synthesis (MIP-1α, MIP-1β, KC, RANTES, MCP-1, and IFN-inducible protein-10), cytokines (IL-8, IL-12, and TNF-α), as well as inducible NO α-synthase and plasminogen activator inhibitor 1 (23). This work has also shown the value of the ratio of pro-inflammatory factors (low molecular weight hyaluronan) to anti-inflammatory factors (high molecular weight hyaluronan). The violation of this ratio with the predominance of pro-inflammatory factors has been possible not only due to the enhanced formation of low molecular weight hyaluronan, but also due to its insufficient elimination. Thus, the cause of "chronization" of the process is a developing imbalance between the phases of the inflammatory reaction, with a predominance of pro-inflammatory phenomena in conditions of insufficient anti-inflammatory and resolving factors At the same time, only destructive-dystrophic processes are possible in a non-vascularized tissue by the analogy with how it initially occurs in articular cartilage. An excellent illustration is a well-known fact that "typical" inflammation develops only in vascular tissues. Therefore, it is considered that in neovascularized tissues, cartilage and cornea, the inflammation begins with the growth of blood vessels. Until vascularization occurs, no inflammation will occur: in the absence of blood vessels, exudation is absent, there is no cell emigration, and, as a result, the cell infiltration is absent (9, 11). As it's known, the main role in angiogenesis is played by endothelial cells, which trigger and control the entire process (10, 12, 21).

CLINICAL SIGNIFICANCE

It is known that there is a large number of studies proving the existence of relationships between angiogenesis and chronic inflammation in many different diseases: psoriasis, diabetes mellitus, Crohn's disease, rheumatoid arthritis, tumors, vessels are also found in the membrane of the hernial protrusion during intervertebral hernia. They demonstrated that the relationship between obesity and osteoarthritis, seemingly non-inflammatory diseases with the inflammation and vascular neoplasm, can be both direct and reverse (10). At the same time, structural changes in the vascular network in the focus of chronic inflammation are characterized not only by the formation of new vessels, but also by remodeling of the existing ones. It was also found that capillaries are capable of structurally and functionally transforming into the venular vessels, with a change in the phenotype of endothelial cells. The functional features were characterized by an increase in the sensitivity of the vessels to the action of the pro-inflammatory mediator P of the substance increasing the permeability of their wall. This feature suggests the possibility of its participation in the formation of the "circulus vitiosus", when small amounts of the inflammatory mediators to which normal vessels do not react, are able to support the increased permeability, promoting exudation and continuing inflammation (10, 13, 26).

Subsequent cellular reactions that occur under the action of chemokines and cytokines support development of the inflammation, through profound structural changes, with the formation of the pathological tissue, the so-called pannus in the cartilage, the underlying bone and the synovial membrane of the joint. A number of studies have demonstrated that the severity of synovitis directly correlates with the clinical symptoms and it also has an unfavorable prognostic value (18, 19).

Another process involved in the formation of new structures is the endothelial-mesenchymal transition, which consists in changing the endotheliocyte phenotype to myofibroblast. A similar phenomenon is observed in the outbreak of chronic (unresolved) inflammation in relation to epithelial cells, which can also transform into mesenchymal cells. The formation of scar tissue and fibrosis in chronic inflammation is associated with this phenomenon (6). The basis of these structural transformations is the change in the functional activity of a variety of cells: endotheliocytes, pericytes, fibroblasts, epithelial cells, macrophages, lymphocytes, and so on. The activation of these cells leads, along with vascular neoplasm, increased wall permeability and edema, to the emigration with infiltration of the tissue with inflammatory cells, an increase in the number and activity of fibroblasts with the development of fibrosis and other degenerative-destructive changes. The result is the formation of a new, non-essential tissue function that differs in its structural and functional characteristics from the normal one (6, 27). As a result, a change in the mechanical properties of the tissue can lead to its traumatization and damage even under the normal loads (16). The combination of these phenomena, in turn, enhances and "chronizes" (prolongs) the local inflammatory response, and, as a result, helps to maintain a systemic inflammatory response. In this way, another "circulus vitiosus", which has already been involved in the progression of the disease, is formed.

The important role of the endothelium should be noted not only in the progression, but also in the completion of inflammation due to the production of anti-inflammatory factors when interacting with polymorphonuclear leukocytes, macrophages and other cells, in replenishing the arising tissue defect and restoring the normal tissue structure (22, 23, 24).

It should be borne in mind that all the above-described phenomena and processes are ambiguous and often contradictory, which create difficulties in the choice and formation

of a medical strategy and tactics. An example of this difficulty is the use of modern pharmacological drugs in the treatment of rheumatoid arthritis. Since rheumatoid arthritis is a chronic inflammatory disease, prostaglandins, leukotrienes (LTB4), and TNFα play an important role in its pathogenesis. The action of modern drugs is aimed at suppressing and preventing their formation, which can help reduce the severity of inflammation and alleviate the symptoms of the disease, but at the same time, their use can lead to a lack of mechanisms for the completion of inflammation (1).

This kind of objection may be applied to other approaches to treatment. This includes serious doubts about the use of angiostatic agents for the treatment of arthritis. In connection with the huge role of angiogenesis in the occurrence of structural changes in the joint and the progression of the disease, it would seem logical to suggest using it in the treatment of angiostatic agents (7). However, these drugs cause only the inhibition of angiogenesis, without affecting the cause of vascular neoplasm and, therefore, ultimately preserve and maintain the achieved vascularization. In connection with the above, it follows that the winning strategy should be to activate the mechanisms of sanogenesis, i.e. in stimulating the completion of inflammation through its resolution. This means that it is necessary to activate the formation of those chemokines and other factors of the completion of inflammation (specialized resolving lipid mediators) that contribute to the reduction of newly formed vessels and the restoration of normal cellular tissue composition (2, 10, 17, 21).

CONCLUSION

The emergence of new foci of inflammation and their transition to a chronic course in patients with comorbid pathology is due, among other things, to the imbalance of counter-regulatory pro-inflammatory, anti-inflammatory and anti-resolving factors of a chronic systemic response. For a successful, controlled completion of the inflammatory process, it is necessary to ensure a systematic approach to the rehabilitation of patients, taking into account the basic medical principles, allowing thebreak of a complex set of pathological circles. The complexity of the impact allows you to potentiate the healing effects at all hierarchical levels in a living organism. It is necessary to take into account the understanding (representation) of the therapeutic effect influence on the phase of inflammation : on the initiation and development phase of the inflammatory response or on the resolution phase of the inflammation.

The etiotropic principle ensures that the impact is directed towards eliminating the cause and effects of its action, which means that it is necessary to take measures to identify and rehabilitate all foci of chronic inflammation in patients with comorbid pathologies, and the effectiveness of the treatment will be directly proportional to the success of each.

The pathogenetic principle ensures that the main mechanisms for the development and progression of the disease are affected, i.e. on the suppression and disconnection of "circulus vitiosus". The difficulty of applying this principle in practice is that among the huge numbers of vicious circles that are formed at all hierarchical levels of the organization, one must be able to choose certain basic, key points of influence as targets, on which the functioning of the basic mechanisms of the disease progression depends. We propose optimization of the choice based on the phenotyping of patient subgroups.

The simultaneous application of these two principles will influence most effectively the phase of the initiation and development of the inflammation.

Transition to chronic inflammation requires creation of conditions to strengthen the mechanisms for resolving the inflammation to eliminate inconsistency between strength of the mechanisms of the initial phase and the phase of completion. Thus, the prerequisite for achieving the desired therapeutic effect is the necessity and necessity of using and applying the sanogenetic principle, which includes measures aimed at the early completion of inflammation and the most complete restoration of damaged tissues.

In turn, in addition to carrying out "anti-inflammatory" therapeutic measures, it is necessary to take into account that the basis of the onset, development and progression of the disease involves non-inflammatory pathogenetic mechanisms, for which you should also use the principles described above for the formation of the treatment algorithm. There is no doubt that throughout the treatment, it is necessary to use the symptomatic treatment that will help speed up the healing process.

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